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EDITORIAL

No need for H_2-antagonists in premedication regimens for paclitaxel infusions: less is more

The theoretical basis for use of histamine 2 (H_2)-receptor inhibitors to prevent hypersensitivity reactions for paclitaxel infusions is weak. This Editorial discusses a clinical study showing that ranitidine is not indicated any more in this setting and puts this in the context of other valuable efforts leaving non-evidence-based interventions behind us.

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MAIN

Even in this era of evidence-based medicine many interventions are still based on scarce or even contradictory evidence. A good example is the use of a histamine 2 (H_2)-receptor antagonist such as ranitidine in premedication schedules for paclitaxel infusions. Hypersensitivity reactions (HSR) to paclitaxel, thought to be mainly due, but not limited to, its solvent Cremophor EL are an important side effect that can be severe or even life-threatening.[1] This side-effect was significantly reduced by premedication consisting of ranitidine in combination with dexamethasone and a histamine-1 (H_1) receptor antagonist. It is however unsure which components of the 3-drug premedication regimen, consisting of dexamethasone and an H_1 and H_2 receptor antagonist, are necessary to prevent these allergic reactions. The theoretical basis for use of ranitidine is the weakest of the 3 medications used while it is known that ranitidine itself may result in hypersensitivity reactions in 0.7% of infusions.[2] Since the added value of an H_2-receptor antagonist has thus far not been systematically studied in the clinic, Cox and colleagues[3] performed a pre-post interventional, non-inferiority study assessing ranitidine prophylaxis for paclitaxel infusions. The results of this practice changing study are presented in this issue of the *British Journal of Cancer*.[3]

All consecutive patients receiving their first cycle of paclitaxel from a single centre were enrolled in this study. All 183 patients in the pre-intervention group received the standard premedication consisting of dexamethasone (10 mg IV), clemastine (2 mg IV) and ranitidine (50 mg IV) and all 183 patients in the sequential post-interventional group received the experimental premedication regimen without ranitidine. HSR of any grade during paclitaxel infusion occurred in 37 (20%) in the pre-interventional group with ranitidine and 22 (12%) in the post-interventional group without ranitidine. Regarding the comparison of—any grade—HSRs, a regimen without ranitidine showed to be non-inferior to the pre-intervention regimen with ranitidine (difference −8.2%, 95% CI −15.0%; −1.4%, $p = 0.046$). The severity of HSRs, the number of paclitaxel dosages and time to first HSR occurrence did not differ between the groups.

The authors should be applauded for their work and this study adds to several others that were done to omit non-evidence based interventions e.g. withholding pre-hydration in patients with stage 3 chronic kidney disease undergoing contrast-enhanced computed tomography[4] and omitting calcium/magnesium infusions to protect against oxaliplatin induced neuropathy.[5] In these examples rigorous prospective Phase 3 studies were used to convince the medical community to stop doing the intervention. Although the study by Cox et al.[3] was, for practical and financial reasons, not randomised, the study was prospective, well balanced and adequately powered, and the results were in line with the preclinical rationale. Therefore, the data are convincing us to refrain from ranitidine, and thus H_2-receptor antagonist premedication in all future patients receiving paclitaxel.

Omitting the unproven intervention not only is cost-efficient, but also reduces risks due to the measures and these studies should therefore be stimulated. In the example of ranitidine and paclitaxel cost-effectiveness has not yet formally been calculated but the authors rightly explain that lower hospital and drug resource use for this frequently used drug will inevitably reduce time and costs. Not only the current ranitidine shortage related to uncertainty about its carcinogenic effects, but also the COVID-19 overall hospital resource shortage adds to the fact that the results of this study are welcomed and ready to be implemented as of now.

The question now is: what is next? It is well known that more than 90% of all paclitaxel related HSRs occur in the first 2 cycles and therefore multiple studies were performed to omit dexamethasone e.g. from cycle 3 onwards in patients who had no prior HSR.[6,7] Given the results of these kind of studies and the broad range of short- and long-term side effects of dexamethasone, discontinuation of dexamethasone beyond cycle 3, especially when used in a weekly schedule, could be considered especially for those with a high risk for steroid-induced side effects, such as patients with diabetes. Also, it remains to be studied what optimal lowest dose of dexamethasone should be used: 10-20 mg seems quite a high dose, especially when given for multiple cycles. The role of H_1-receptor antagonist beyond cycle 3 also needs to be studied in the future as drowsiness is a common side effect of these drugs and for the same reasons of cost-effectiveness as discussed earlier.

The novel taxanes, not formulated in Cremophor EL such as docetaxel and more recently cabazitaxel (both formulated in polysorbate 80) have a much lower risk of HSRs: the optimal premedication regimen should be re-evaluated for these taxanes as well. A very high dose of dexamethasone is advised for docetaxel, up to 8 mg twice daily for 3 days. Therefore, we are currently performing a dexamethasone dose de-escalation study (NCT02776436) which should lead to a confirmatory larger trial. Ultimately newer taxanes with minimal chance of HSRs, such as albumin bound nab-paclitaxel, should pave the way to a safe and HSR-free future for this important class chemotherapeutics in oncology. Meanwhile, as long as paclitaxel is still one of the most frequently used taxanes, the study by Cox et al.[3] has shown us how to improve its use in clinical practice: less is more.

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